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(54) Title: ANALOGS OF PARATHYROID HORMONE

(57) Abstract

Peptide variants of fragment of parathyroid hormone (PTH) or parathyroid hormone–related protein (PTHrP), in which at least one of the amino acid residues is replaced with Acc.

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ANALOGS OF PARATHYROID HORMONE

Cross Reference To Related Applications

This application is a counterpart of U.S. application 08/779,768 filed January 7, 1997, now pending.

Background of the Invention

Parathyroid hormone ("PTH") is a polypeptide produced by the parathyroid glands. The mature circulating form of the hormone is comprised of 84 amino acid residues. The biological action of PTH can be reproduced by a peptide fragment of its N-terminus (e.g. amino acid residues 1 through 34). Parathyroid hormone-related protein ("PTHrP") is a 139 to 173 amino acid-protein with N-terminal homology to PTH. PTHrP shares many of the biological effects of PTH including binding to a common PTH/PTHrP receptor. Tregear, et al., Endocrinol., 93:1349 (1983). PTH peptides from many different sources, e.g., human, bovine, rat, chicken, have been characterized. Nissenson, et al., Receptor, 3:193 (1993).

PTH has been shown to both improve bone mass and quality. Dempster, et al., Endocrine Rev., 14:690 (1993); and Riggs, Amer. J. Med., 91 (Suppl. 5B):37S (1991). The anabolic effect of intermittently administered PTH has been observed in osteoporotic men and women either with or without concurrent antiresorptive therapy. Slovik, et al., J. Bone Miner. Res., 1:377 (1986); Reeve, et al., Br. Med. J., 301:314 (1990); and Hesch, R-D., et al., Calcif. Tissue Int'l, 44:176 (1989).

Summary of the Invention

In one aspect, the invention features a peptide of the formula:

$$R_1$$
$$\backslash$$
$$A_1\text{-Val-}A_3\text{-Glu-}A_5\text{-Gln-}A_7\text{-}A_8\text{-His-Asn-}A_{11}\text{-}A_{12}\text{-Lys-His-}A_{15}\text{-}$$
$$/$$
$$R_2$$

$$A_{16}\text{-}A_{17}\text{-}A_{18}\text{-}A_{19}\text{-Arg-}A_{21}\text{-}A_{22}\text{-}A_{23}\text{-}A_{24}\text{-Arg-Lys-}A_{27}\text{-}A_{28}\text{-}A_{29}\text{-}$$

$$A_{30}\text{-}A_{31}\text{-}A_{32}\text{-}A_{33}\text{-}A_{34}\text{-}R_3,$$

wherein

A_1 is Ser, Ala, or Dap;

A_3 is Ser, Thr, or Aib;

A_5 is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe or p-X-Phe, in which X is OH, a halogen, or CH_3;

A_7 is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, or p-X-Phe in which X is OH, a halogen, or CH_3;

A_8 is Met, Nva, Leu, Val, Ile, Cha, Acc, or Nle;

A_{11} is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe or p-X-Phe in which X is OH, a halogen, or CH_3;

A_{12} is Gly, Acc, or Aib;

A_{15} is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, or p-X-Phe in which X is OH, a halogen, or CH_3;

A_{16} is Ser, Asn, Ala, or Aib;

A_{17} is Ser, Thr, or Aib;

A_{18} is Met, Nva, Leu, Val, Ile, Nle, Acc, Cha, or Aib;

A_{19} is Glu or Aib;

A_{21} is Val, Acc, Cha, or Met;

A_{22} is Acc or Glu;

A_{23} is Trp, Acc, or Cha;

A_{24} is Leu, Acc, or Cha;

A_{27} is Lys, Aib, Leu, hArg, Gln, Acc, or Cha;

A_{28} is Leu, Acc, or Cha;

A_{29} is Glu, Acc, or Aib;

A_{30} is Asp or Lys;

A_{31} is Val, Leu, Nle, Acc, Cha, or deleted;

A_{32} is His or deleted;

A_{33} is Asn or deleted;

A_{34} is Phe, Tyr, Amp, Aib, or deleted;

each of R_1 and R_2 is, independently, H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{7-20} phenylalkyl, C_{11-20} napthylalkyl, C_{1-12} hydroxyalkyl, C_{2-12} hydroxyalkenyl, C_{7-20} hydroxyphenylalkyl, or C_{11-20} hydroxynapthylalkyl; or one and only one of R_1 and R_2 is COE_1 in which E_1 is C_{1-12} alkyl, C_{2-12} alkenyl, C_{7-20} phenylalkyl, C_{11-20} napthylalkyl, C_{1-12} hydroxyalkyl, C_{2-12} hydroxyalkenyl, C_{7-20} hydroxyphenylalkyl, or C_{11-20} hydroxynapthylalkyl; and

R_3 is OH, NH_2, C_{1-12} alkoxy, or NH-Y-CH_2-Z in which Y is a C_{1-12} hydrocarbon moiety and Z is H, OH, CO_2H, or $CONH_2$;

provided that at least one of A_5, A_7, A_8, A_{11}, A_{12}, A_{15}, A_{18}, A_{21}, A_{22}, A_{23}, A_{24}, A_{27}, A_{28}, A_{29}, and A_{31} is Acc; or a pharmaceutically acceptable salt thereof.

The following are examples of the peptides of the invention covered by the above formula: [$Ahc^{7,11}$]hPTH(1-34)NH_2; [$Ahc^{7,11}$, $Nle^{8,18}$, Tyr^{34}]hPTH(1-34)NH_2; [Ahc^{11}]hPTH(1-34)NH_2; [$Ahc^{7,11,15}$]hPTH(1-34)NH_2; [Ahc^{7}]hPTH(1-34)NH_2; [Ahc^{23}]hPTH(1-34)NH_2; [Ahc^{24}]hPTH(1-34)NH_2; [$Nle^{8,18}$, Ahc^{27}]hPTH(1-34)NH_2; [Ahc^{28}]hPTH(1-34)NH_2; [Ahc^{31}]hPTH(1-34) NH_2; [$Ahc^{24,28,31}$]hPTH(1-34)NH_2; [$Ahc^{24,28,31}$, Lys^{30}]hPTH(1-34) NH_2; [$Ahc^{28,31}$]hPTH(1-34)NH_2; [Ahc^{15}]hPTH(1-34)NH_2; [$Ahc^{24,27}$, Aib^{29}, Lys^{30}]hPTH(1-34)NH_2; [$Ahc^{24,27}$, Aib^{29}, Lys^{30}, Leu^{31}]hPTH (1-34)NH_2; [Ahc^{5}]hPTH(1-34)NH_2; [Ahc^{12}]hPTH(1-34)NH_2; [Ahc^{27}] hPTH(1-34)NH_2;

[Ahc^{29}]hPTH(1-34)NH_2; [$Ahc^{24,27}$]hPTH(1-34)NH_2; [$Ahc^{24,27}$, Aib^{29}]hPTH(1-34)NH_2; [Ahc^{24}, Aib^{29}]hPTH(1-34)NH_2; [Ahc^{27}, Aib^{29}]hPTH(1-34)NH_2; [Ahc^{18}]hPTH(1-34)NH_2; [Ahc^{8}]hPTH (1-34)NH_2; [$Ahc^{18,27}$, Aib^{29}]hPTH (1-34)NH_2; [$Ahc^{18,24,27}$, Aib^{29}] hPTH(1-34)NH_2; [Ach]^{22}hPTH(1-34)NH_2; or [Ahc^{22}, Aib^{29}]hPTH(1-34)NH_2; [Ahc^{22}, Leu^{27}, Aib^{29}]hPTH(1-34)NH_2; [Ahc^{24}, Leu^{27}, Aib^{29}] hPTH(1-34)NH_2; or a pharmaceutically acceptable salt thereof.

In another aspect, the invention features a peptide of the formula:

$$\begin{matrix} R_1 \diagdown \\ \quad A_1\text{-Val-}A_3\text{-Glu-}A_5\text{-Gln-}A_7\text{-}A_8\text{-His-}A_{10}\text{-}A_{11}\text{-}A_{12}\text{-Lys-}A_{14}\text{-}A_{15}\text{-} \\ R_2 \diagup \end{matrix}$$

$$A_{16}\text{-}A_{17}\text{-}A_{18}\text{-}A_{19}\text{-Arg-Arg-}A_{22}\text{-}A_{23}\text{-}A_{24}\text{-}A_{25}\text{-}A_{26}\text{-}A_{27}\text{-}A_{28}\text{-}$$

$$A_{29}\text{-}A_{30}\text{-}A_{31}\text{-}A_{32}\text{-}A_{33}\text{-}A_{34}\text{-}R_3$$

wherein

A_1 is Ala, Ser, or Dap;

A_3 is Ser or Aib;

A_5 is His, Ile, Acc, or Cha;

A_7 is Leu, Cha, Nle, β-Nal, Trp, Pal, Acc, Phe, or p-X-Phe in which X is OH, a halogen, or CH_3;

A_8 is Leu, Met, Acc, or Cha;

A_{10} is Asp or Asn;

A_{11} is Lys, Leu, Cha, Acc, Phe, or β-Nal;

A_{12} is Gly, Acc, or Aib;

A_{14} is Ser or His;

A_{15} is Ile, Acc, or Cha;

A_{16} is Gln or Aib;

A_{17} is Asp or Aib;

A_{18} is Leu, Aib, Acc, or Cha;

A_{19} is Arg or Aib;

A_{22} is Phe, Glu, Aib, Acc, or Cha;

A_{23} is Phe, Leu, Lys, Acc, or Cha;

A_{24} is Leu, Lys, Acc, or Cha;

A_{25} is His, Lys, Aib, Acc, or Glu;

A_{26} is His, Aib, Acc, or Lys;

A_{27} is Leu, Lys, Acc, or Cha;

A_{28} is Ile, Leu, Lys, Acc, or Cha;

A_{29} is Ala, Glu, Acc, or Aib;

A_{30} is Glu, Leu, Nle, Cha, Aib, Acc, or Lys;

A_{31} is Ile, Leu, Cha, Lys, Acc, or deleted;

A_{32} is His or deleted;

A_{33} is Thr or deleted;

A_{34} is Ala or deleted;

each of R_1 and R_2 is, independently, H, C_{1-12} alkanyl, C_{7-20} phenylalkyl, C_{11-20} napthyalkyl, C_{1-12}, hydroxyalkyl, C_{2-12} hydroxyalkenyl, C_{7-20} hydroxyphenylalkyl, or C_{11-20} hydroxynapthylalkyl; or one and only one of R_1 and R_2 is COE_1 in which E_1 is C_{1-12} alkyl, C_{2-12} alkyl, C_{2-12} alkenyl, C_{7-20} phenylalkyl, C_{11-20} napthylalkyl, C_{1-12} hydroxyalkyl, C_{2-12} hydroxyalkenyl, C_{7-20} hydroxyphenylalkyl, or C_{11-20} hydroxynapthylalkyl; and

R_3 is OH, NH_2, C_{1-12} alkoxy, or NH-Y-CH_2-Z in which Y is a C_{1-12} hydrocarbon moiety and Z is H, OH, CO_2H or $CONH_2$;

provided that at least one of A_5, A_7, A_8, A_{11}, A_{12}, A_{15}, A_{18}, A_{22}, A_{23}, A_{24}, A_{25}, A_{26}, A_{27}, A_{28}, A_{29}, A_{30}, or A_{31} is Acc; or a pharmaceutically acceptable salt thereof.

The following are examples of the peptides of the invention covered by the above formula:

[Glu$^{22, 25}$, Leu$^{23, 28}$, Lys$^{26, 30}$, Aib^{29}, Ahc^{31}]hPTHrP(1-34)NH_2;

[Glu$^{22, 25}$, Ahc^{23}, Lys$^{26, 30}$, Leu$^{28, 31}$, Aib^{29}]hPTHrP(1-34)NH_2;

[Glu$^{22, 25}$, Leu$^{23, 28, 31}$, Lys$^{26, 30}$, Ahc^{27}, Aib^{29}]hPTHrP(1-34)NH_2;

[Glu$^{22, 25, 29}$, Leu$^{23, 28, 31}$, Lys^{26}, Ahc^{30}]hPTHrP(1-34)NH_2; [Cha^{22}, Leu$^{23, 28, 31}$, Glu^{25}, Lys$^{26, 30}$, Ahc^{27}, Aib^{29}]hPTHrP(1-34)NH_2;

[Glu$^{22, 25}$, Leu$^{23, 28, 31}$, Ahc^{24}, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2;

[Glu$^{22, 29}$, Leu$^{23, 28, 31}$, Aib^{25}, Lys$^{26, 30}$, Ahc^{27}]hPTHrP(1-34)NH_2;

[Glu^{22}, Leu$^{23, 28, 31}$, Aib$^{25, 29}$, Lys$^{26, 30}$, Ahc^{27}]hPTHrP(1-34)NH_2;

[Ahc^{22}, Leu$^{23, 28, 31}$, Glu^{25}, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Leu$^{23, 31}$, Lys$^{26, 30}$, Ahc^{28}, Aib^{29}]hPTHrP(1-34)NH_2; [Cha^{22}, Ahc^{23}, Glu^{25}, Lys$^{26, 30}$, Leu$^{28, 31}$, Aib^{29}]hPTHrP(1-34)NH_2; [Ahc$^{22, 24, 27}$, Leu$^{23, 28, 31}$, Glu^{25}, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2; [Cha^{22}, Leu$^{23, 28, 31}$, Ahc$^{24, 27}$, Glu^{25}, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Leu$^{23, 28, 31}$, Ahc$^{24, 27}$, Lys$^{25, 26}$, Aib^{29}]hPTHrP(1-34)NH_2; [Ahc$^{18, 24, 27}$, Glu^{22}, Cha^{23}, Lys$^{25, 26}$, Leu^{28}, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Cha^{23}, Ahc^{24}, Lyc$^{25, 26}$, Leu^{28}, Aib^{29}]hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Leu$^{23, 28, 31}$, Lys^{26}, Ahc^{27}, Aib^{29}, Nle^{30}]hPTHrP(1-34)NH_2; [Ser^{1}, Ile^{5}, Cha$^{7, 11}$, Met^{8}, Asn^{10}, His^{14}, Glu$^{22, 25}$, Leu$^{23, 28, 31}$, Lys$^{26, 30}$, Ahc^{27}, Aib^{29}]hPTHrP(1-34)NH_2; [Ser^{1}, Ile^{5}, Met^{8}, Asn^{10}, Leu$^{11, 23, 28, 31}$, His^{14}, Cha^{15}, Glu$^{22, 25}$, Lys$^{26, 30}$, Ahc^{27}, Aib^{29}]hPTHrP(1-34)NH_2; [Cha^{22}, Ahc^{23}, Glu^{25}, Lys$^{26, 30}$, Leu$^{28, 31}$, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Ahc^{23}, Aib$^{25, 29}$, Lys$^{26, 30}$, Leu$^{28, 31}$]hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Leu$^{23, 28, 31}$, Lys$^{26, 30}$, Ahc^{29}]hPTHrP(1-34)NH_2; [Cha^{22}, Leu$^{23, 28, 31}$, Ahc^{24}, Glu^{25}, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2; [Cha^{22}, Leu$^{23, 28, 31}$, Ahc$^{24, 27}$, Glu^{25}, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Leu$^{23, 28, 31}$, Ahc$^{24, 27}$, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2; [Ahc$^{22, 24, 27}$, Leu$^{23, 28, 31}$, Glu^{25}, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2; [Cha^{22}, Leu$^{23, 28, 31}$, Aib$^{25, 29}$, Lys$^{26, 30}$, Ahc^{27}]hPTHrP(1-34)NH_2; [Ahc$^{22, 27}$, Leu$^{23, 28, 31}$, Aib$^{25, 29}$, Lys$^{26, 30}$]hPTHrP(1-34)NH_2; [Glu^{22}, Leu$^{23, 28, 31}$, Ahc$^{24, 27}$, Lys$^{25, 26, 30}$, Aib^{29}]hPTHrP 1-34)NH_2; [Glu^{22}, Leu$^{23, 28}$, Ahc$^{24, 27}$, Lys$^{25, 26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Cha^{23}, Ahc$^{24, 27}$, Lys$^{25, 26, 30}$, Leu^{28}, Aib^{29}]hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Cha^{23}, Ahc$^{24, 27}$, Lys$^{26, 30}$, Leu$^{28, 31}$, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Cha^{23}, Ahc$^{24, 27}$, Lys$^{25, 26, 30}$, Leu$^{28, 31}$, Aib^{29}]hPTHrP(1-34) NH_2; [Glu^{22}, Leu$^{23, 28, 31}$, Ahc$^{24, 27}$, Lys$^{25, 26}$, Aib^{29}]hPTHrP(1-34) NH_2; [Glu^{22}, Leu$^{23, 28}$, Ahc$^{24, 27}$, Lys$^{25, 26}$, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Cha^{23}, Ahc$^{24, 27}$, Lys$^{25, 26}$, Leu$^{28, 31}$, Aib^{29}]hPTHrP(1-34) NH_2; [Glu^{22}, Cha^{23}, Ahc$^{24, 27}$, Lys$^{25, 26}$, Leu^{28}, Aib^{29}]hPTHrP 1-34) NH_2; [Glu^{22}, Leu$^{23, 28}$, Lys$^{25, 26}$, Ahc^{27}, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Leu$^{23, 28, 31}$, Lys$^{25, 26}$, Ahc^{27}, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Leu$^{23, 28, 31}$, Lys$^{25, 26, 30}$,

Ahc^{27}, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Leu$^{23, 28}$, Lys$^{25, 26, 30}$, Ahc^{27}, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Cha^{23}, Ahc^{24}, Lys$^{25, 26}$, Leu^{28}, Aib^{29}]hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Leu$^{23, 28, 31}$, Lys^{26}, Aib^{29}, Ahc^{30}]hPTHrP(1-34)NH_2; [Aib$^{22, 29}$, Leu$^{23, 28, 31}$, Glu^{25}, Lys$^{26, 30}$]hPTHrP(1-34)NH_2; [Cha^{22}, Ahc^{23}, Glu$^{25, 29}$, Lys$^{26, 30}$, Leu$^{28, 31}$]hPTHrP(1-34)NH_2; [Cha^{22}, Leu$^{23, 28, 31}$, Ahc^{24}, Glu$^{25, 29}$, Lys$^{26, 30}$]hPTHrP(1-34)NH_2; [Cha^{22}, Leu$^{23, 28, 31}$, Glu$^{25, 29}$, Lys$^{26, 30}$, Ahc^{27}]hPTHrP(1-34)NH_2; [Cha^{22}, Leu$^{23, 31}$, Glu$^{25, 29}$, Lys$^{26, 30}$, Ahc^{28}]hPTHrP(1-34)NH_2; [Cha^{22}, Leu$^{23, 28, 31}$, Glu$^{25, 29}$, Lys^{26}, Ahc^{30}]hPTHrP(1-34)NH_2; [Cha^{22}, Leu$^{23, 28}$, Glu$^{25, 29}$, Lys$^{26, 30}$, Ahc^{31}]hPTHrP(1-34)NH_2; [Glu$^{22, 29}$, Ahc^{23}, Aib^{25}, Lys$^{26, 30}$, Leu$^{28, 31}$]hPTHrP(1-34)NH_2; [Ahc^{22}, Leu$^{23, 28, 31}$, Aib^{25}, Lys$^{26, 30}$, Glu^{29}]hPTHrP(1-34)NH_2; [Glu$^{22, 29}$, Leu$^{23, 28, 31}$, Ahc^{24}, Aib^{25}, Lys$^{26, 30}$]hPTHrP(1-34)NH_2; [Glu$^{22, 29}$, Leu$^{23, 31}$, Aib^{25}, Lys$^{26, 30}$, Ahc^{28}] hPTHrP(1-34)NH_2; [Glu$^{22, 29}$, Leu$^{23, 28}$, Aib^{25}, Lys$^{26, 30}$, Ahc^{31}] hPTHrP(1-34)NH_2; [Glu$^{22, 29}$, Leu$^{23, 28, 31}$, Aib^{25}, Lys^{26}, Ahc^{30}] hPTHrP(1-34)NH_2; [Glu$^{22, 25, 29}$, Leu$^{23, 28, 31}$, Lys^{26}, Ahc^{27}, Aib^{30}] hPTHrP(1-34)NH_2; [Glu$^{22, 25, 29}$, Leu$^{23, 28, 31}$, Ahc^{24}, Lys^{26}, Aib^{30}] hPTHrP(1-34)NH_2; [Ahc^{22}, Leu$^{23, 28, 31}$, Glu$^{25, 29}$, Lys^{26}, Aib^{30}] hPTHrP(1-34)NH_2; [Ahc^{22}, Leu$^{23, 28}$, Glu$^{25, 29}$, Lys$^{26, 30, 31}$]hPTHrP(1-34)NH_2; [Glu$^{22, 25, 29}$, Leu$^{23, 28}$, Lys$^{26, 31}$, Ahc^{30}]hPTHrP(1-34)NH_2; [Glu$^{22, 25, 29}$, Leu$^{23, 28}$, Lys$^{26, 30, 31}$, Ahc^{27}]hPTHrP(1-34) NH_2; [Ahc^{22}, Cha^{23}, Glu^{25}, Lys$^{26, 30}$, Leu$^{28, 31}$, Aib^{29}]hPTHrP(1-34)NH_2; [Ahc^{22}, Cha^{23}, Lys$^{25, 26, 30}$, Leu$^{28, 31}$, Aib^{29}]hPTHrP(1-34)NH_2; [Ahc^{22}, Cha^{23}, Lys$^{25, 26}$, Leu$^{28, 31}$, Aib^{29}]hPTHrP(1-34)NH_2; [Ahc^{22}, Leu$^{23, 28}$, Lys$^{25, 26}$, Aib^{29}]hPTHrP(1-34)NH_2; [Ahc^{22}, Leu$^{23, 28}$, Arg^{25}, Lys^{26}, Aib^{29}]hPTHrP(1-34)NH_2; [Ahc$^{22, 24}$, Leu$^{23, 28, 31}$, Glu^{25}, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2; [Ahc$^{22, 24}$, Leu$^{23, 28, 31}$, Lys$^{25, 26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2; [Ahc$^{22, 24}$, Leu$^{23, 28, 31}$, Lys$^{25, 26}$, Aib^{29}] hPTHrP(1-34)NH_2; [Ahc$^{22, 24}$, Leu$^{23, 28}$, Lys$^{25, 26}$, Aib^{29}]hPTHrP(1-34)NH_2; [Ahc$^{22, 24}$, Leu$^{23, 28}$, Arg^{25}, Lys^{26}, Aib^{29}]hPTHrP(1-34)NH_2;

[Glu^{22}, Leu$^{23, 28, 31}$, Ahc^{24}, Lys$^{25, 26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2;

[Glu^{22}, Leu$^{23, 28, 31}$, Ahc^{24}, Lys$^{25, 26}$, Aib^{29}]hPTHrP(1-34)NH_2;

[Glu^{22}, Leu$^{23, 28}$, Ahc^{24}, Lys$^{25, 26}$, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Leu$^{23, 28, 31}$, Ahc^{24}, Arg^{25}, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Leu$^{23, 28, 31}$, Ahc^{24}, Arg^{25}, Lys^{26}, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Leu$^{23, 28}$, Ahc^{24}, Arg^{25}, Lys^{26}, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Ahc^{23}, Aib$^{25, 29}$, Lys$^{26, 30}$, Leu$^{28, 31}$]hPTHrP(1-34)NH_2; [Glu^{22}, Ahc^{23}, Aib$^{25, 29}$, Lys^{26}, Leu^{28}]hPTHrP(1-34)NH_2; [Glu^{22}, Ahc$^{23, 31}$, Aib$^{25, 29}$, Lys^{26}, Leu^{28}]hPTHrP(1-34)NH_2; [Glu^{22}, Leu$^{23, 28}$, Aib$^{25, 29}$, Lys$^{26, 30}$, Ahc^{31}]hPTHrP(1-34)NH_2; [Glu^{22}, Leu$^{23, 28}$, Aib$^{25, 29}$, Lys^{26}, Ahc^{31}]hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Leu$^{23, 28}$, Ahc$^{24, 31}$, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2; or [Glu^{22}, Leu$^{23, 28}$, Ahc$^{24, 31}$, Lys$^{25, 26}$, Aib^{29}]hPTHrP(1-34)NH_2; [Glu^{22}, Leu$^{23, 28, 31}$, Ahc^{24}, Aib$^{25, 29}$, Lys$^{26, 30}$]hPTHrP(1-34)NH_2; or a pharmaceutically acceptable salt thereof.

The invention also features peptides of the following formulae: [Cha$^{22, 23}$, Glu^{25}, Lys$^{26, 30}$, Leu^{28}, Aib^{29}]hPTHrP(1-34)NH_2; [Cha$^{22, 23}$, Glu^{25}, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34) NH_2; [Glu$^{22, 25}$, Leu$^{23, 28, 31}$, Lys^{26}, Aib^{29}, Nle^{30}]hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Leu$^{23, 28, 30, 31}$, Lys^{26}, Aib^{29}]hPTHrP(1-34)NH_2; [Glu$^{22, 25, 29}$, Leu$^{23, 28, 30, 31}$, Lys^{26}]hPTHrP(1-34)NH_2; [Glu$^{22, 25, 29}$, Leu$^{23, 28, 31}$, Lys^{26}, Nle^{30}]hPTHrP(1-34)NH_2; [Ser^{1}, Ile^{5}, Met^{8}, Asn^{10}, Leu$^{11, 23, 28, 31}$, His^{14}, Cha^{15}, Glu$^{22, 25}$, Lys$^{26, 30}$, Aib^{29}]hPTHrP (1-34)NH_2; [Glu$^{22, 25}$, Cha^{23}, Lys^{26}, Leu$^{28, 31}$, Aib^{29}, Nle^{30}]hPTHrP (1-34)NH_2; [Cha$^{22, 23}$, Glu^{25}, Lys$^{26, 30}$, Leu$^{28, 31}$, Aib^{29}]hPTHrP(1-34) NH_2; [Cha^{22}, Leu$^{23, 28, 31}$, Glu$^{25, 29}$, Lys^{26}, Nle^{30}]hPTHrP(1-34)NH_2; [Cha$^{7, 11, 15}$]hPTHrP(1-34)NH_2; [Cha$^{7, 8, 15}$]hPTHrP(1-34)NH_2; [Glu^{22}, Cha^{23}, Aib$^{25, 29}$, Lys$^{26, 30}$, Leu$^{28, 31}$]hPTHrP(1-34)NH_2; [Glu^{22}, Cha^{23}, Aib$^{25, 29}$, Lys^{26}, Leu^{28}]hPTHrP(1-34)NH_2; [Glu^{22}, Leu$^{23, 28}$, Aib$^{25, 29}$, Lys^{26}]hPTHrP(1-34)NH_2; [Aib^{29}]hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Cha^{23}, Lys^{26}, Leu$^{28, 31}$, Aib^{29}, Nle^{30}]hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Cha^{23}, Lys$^{26, 30}$, Aib^{29}, Leu^{31}]hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Leu$^{23, 28, 31}$, Lys^{26}, Aib$^{29, 30}$]hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Leu$^{23, 28, 31}$, Lys^{26}, Aib^{29}]hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Leu$^{23, 28, 31}$, Aib$^{26, 29}$, Lys^{30}] hPTHrP(1-34)NH_2; [Glu$^{22, 25}$, Cha^{23}, Lys$^{26, 30}$, Leu$^{28, 31}$,

Aib[29]] hPTHrP(1-34)NH_2; [Glu[22, 25], Cha[23], Lys[26, 30], Aib[29]]hPTHrP(1-34) NH_2; [Glu[22, 25], Cha[23], Lys[26, 30], Leu[28], Aib[29]]hPTHrP(1-34)NH_2; or [Leu[27], Aib[29]]hPTH(1-34)NH_2; or a pharmaceutically acceptable salt thereof.

With the exception of the N-terminal amino acid, all abbreviations (e.g. Ala or A_1) of amino acids in this disclosure stand for the structure of -NH-CH(R)-CO-, wherein R is a side chain of an amino acid (e.g., CH_3 for Ala). For the N-terminal amino acid, the abbreviation stands for the structure of =N-CH(R)-CO-, wherein R is a side chain of an amino acid. β-Nal, Nle, Dap, Cha, Nva, Amp, Pal, Ahc, and Aib are the abbreviations of the following α-amino acids: β-(2-naphthyl)alanine, norleucine, α,β-diaminopropionic acid, cyclohexylalanine, norvaline, 4-amino-phenylalanine, β-(3-pyridinyl)alanine, 1-amino-1-cyclo-hexanecarboxylic acid, and α-aminoisobutyric acid, respectively. What is meant by Acc is an amino acid selected from the group of 1-amino-1-cyclopropanecarboxylic acid;
1-amino-1-cyclobutanecarboxylic acid;
1-amino-1-cyclopentanecarboxylic acid;
1-amino-1-cyclohexanecarboxylic acid;
1-amino-1-cycloheptanecarboxylic acid;
1-amino-1-cyclooctanecarboxylic acid; and
1-amino-1-cyclononanecarboxylic acid. In the above formula, hydroxyalkyl, hydroxyphenyl-alkyl, and hydroxynaphthylalkyl may contain 1-4 hydroxy substituents. Also, COE_1 stands for -C=O·E_1. Examples of -C=O·E_1 include, but are not limited to, acetyl and phenylpropionyl.

A peptide of this invention is also denoted herein by another format, e.g., [Ahc[7, 11]]hPTH(1-34)NH_2, with the substituted amino acids from the natural sequence placed between the second set of brackets (e.g., Ahc[7] for Leu[7], and Ahc[11] for Leu[11] in hPTH). The abbreviation hPTH stands

for human PTH, hPTHrP for human PTHrP, rPTH for rat PTH, and bPTH for bovine PTH. The numbers between the parentheses refer to the number of amino acids present in the peptide (e.g., hPTH(1-34) is amino acids 1 through 34 of the peptide sequence for human PTH). The sequences for hPTH(1-34), hPTHrP(1-34), bPTH(1-34), and rPTH(1-34) are listed in Nissenson, et al., Receptor, 3:193 (1993). The designation "NH_2" in PTH(1-34)NH_2 indicates that the C-terminus of the peptide is amidated. PTH(1-34), on the other hand, has a free acid C-terminus.

Each of the peptides of the invention is capable of stimulating the growth of bone in a subject (i.e., a mammal such as a human patient). Thus, it is useful in the treatment of osteoporosis and bone fractures when administered alone or concurrently with antiresorptive therapy, e.g., bisphosphonates and calcitonin.

The peptides of this invention can be provided in the form of pharmaceutically acceptable salts. Examples of such salts include, but are not limited to, those formed with organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methanesulfonic, toluenesulfonic, or pamoic acid), inorganic acids (e.g., hydrochloric acid, sulfuric acid, or phosphoric acid), and polymeric acids (e.g., tannic acid, carboxymethyl cellulose, polylactic, polyglycolic, or copolymers of polylactic-glycolic acids).

A therapeutically effective amount of a peptide of this invention and a pharmaceutically acceptable carrier substance (e.g., magnesium carbonate, lactose, or a phospholipid with which the therapeutic compound can form a micelle) together form a therapeutic composition (e.g., a pill, tablet, capsule, or liquid) for administration (e.g., orally, intravenously, transdermally, pulmonarily, vaginally, subcutaneously, nasally, iontophoretically, or by intratracheally) to a subject. The pill, tablet, or

capsule that is to be administered orally can be coated with a substance for protecting the active composition from the gastric acid or intestinal enzymes in the stomach for a period of time sufficient to allow it to pass undigested into the small intestine. The therapeutic composition can also be in the form of a biodegradable or nonbiodegradable sustained release formulation for subcutaneous or intramuscular administration. See, e.g., U.S. Patents 3,773,919 and 4,767,628 and PCT Application No. WO 94/15587. Continuous administration can also be achieved using an implantable or external pump (e.g., INFUSAID™ pump). The administration can also be conducted intermittently, e.g., single daily injection, or continuously at a low dose, e.g., sustained release formulation.

The dose of a peptide of the present invention for treating the above-mentioned diseases or disorders varies depending upon the manner of administration, the age and the body weight of the subject, and the condition of the subject to be treated, and ultimately will be decided by the attending physician or veterinarian.

Also contemplated within the scope of this invention is a peptide covered by the above generic formula for use in treating diseases or disorders associated with deficiency in bone growth or the like, e.g., osteoporosis or fractures.

Other features and advantages of the present invention will be apparent from the detailed description and from the claims.

Detailed Description of the Invention

Based on the description herein, the present invention can be utilized to its fullest extent. The following specific examples are to be construed as merely illustrative, and not limitative of the remainder of the

disclosure in any way whatsoever. Further, all publications cited herein are incorporated by reference.

Structure

PTH(1-34) and PTHrP(1-34) have been reported to have two amphophilic alpha helical domains. See, e.g., Barden, et al., Biochem., 32:7126 (1992). The first α-helix is formed between amino acid residues 4 through 13, while the second α-helix is formed between amino acid residues 21 through 29. Some peptides of this invention contain the substitution of Acc for one or more residues within or near these two regions of PTH(1-34) and PTHrP(1-34), e.g., Ahc^{7} and Ahc^{11} within the first α-helix or Ahc^{27} and Ahc^{28} within the second α-helix.

Synthesis

The peptides of the invention can be prepared by standard solid phase synthesis. See, e.g., Stewart, J.M., et al., Solid Phase Synthesis (Pierce Chemical Co., 2d ed. 1984). The following is a description of how [$Glu^{22,25}$, $Leu^{23,28}$, $Lys^{26,30}$, Aib^{29}, Ahc^{31}]hPTH(1-34)NH_2 was prepared. Other peptides of the invention can be prepared in an analogous manner by a person of ordinary skill in the art.

1-[N-tert-Butoxycarbonyl-amino]-1-cyclohexane-carboxylic acid(Boc-Ahc-OH) was synthesized as follows:

19.1 g (0.133 mol) of 1-amino-1-cyclohexanecarboxylic acid (Acros Organics, Fisher Scientific, Pittsburgh, PA) was dissolved in 200 ml of dioxane and 100 ml of water. To it was added 67 mg of 2N NaOH. The solution was cooled in an ice-water bath. 32.0 g (0.147 mol) of di-tert-butyl-dicarbonate was added to this solution. The reaction mixture was stirred overnight at room temperature. Dioxane was then removed under reduced pressure. 200 ml of ethyl acetate was

added to the remaining aqueous solution. The mixture was cooled in an ice-water bath. The pH of the aqueous layer was adjusted to about 3 by adding 4N HCl. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (1 x 100 ml). Two organic layers were combined and washed with water (2 x 150 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. The residue was recrystallized in ethyl acetate/hexanes. 9.2 g of a pure product was obtained. 29% yield. Other protected Acc amino acids can be prepared in an analogous manner by a person or ordinary skill in the art.

The peptide was synthesized on an Applied Biosystems (Foster City, CA) model 430A peptide synthesizer which was modified to do accelerated Boc-chemistry solid phase peptide synthesis. See Schnoize, et al., Int. J. Peptide Protein Res., 90:180 (1992). 4-Methylbenz-hydrylamine (MBHA) resin (Peninsula, Belmont, CA) with the substitution of 0.93 mmol/g was used. The Boc amino acids (Bachem, CA, Torrance, CA; Nova Biochem., LaJolla, CA) were used with the following side chain protection: Boc-Ala-OH, Boc-Arg(Tos)-OH, Boc-Asp(OcHex)-OH, Boc-Glu(OcHex)-OH, Boc-His(DNP)-OH, Boc-Val-OH, Boc-Leu-OH, Boc-Gly-OH, Boc-Gln-OH, Boc-Ile-OH, Boc-Lys(2ClZ)-OH, Boc-Ahc-OH, Boc-Thr(Bzl)-OH, Boc-Ser(Bzl)-OH; and Boc-Aib-OH. The synthesis was carried out on a 0.14 mmol scale. The Boc groups were removed by treatment with 100% TFA for 2 x 1 min. Boc amino acids (2.5 mmol) were pre-activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF and were coupled without prior neutralization of the peptide-resin TFA salt. Coupling times were 5 min except for the Boc-Aib-OH, and its following residue Boc-Leu-OH, and Boc-Ahc-OH, and its following residue Boc-Lys(2Clz)-OH, wherein the coupling times for these four residues were 2 hrs.

At the end of the assembly of the peptide chain, the resin was treated with a solution of 20% mercaptoethanol/10% DIEA in DMF for 2 x 30 min. to remove the DNP group on the His side chain. The N-terminal Boc group was then removed by treatment with 100% TFA for 2 x 2 min. The partially-deprotected peptide-resin was washed with DMF and DCM and dried under reduced pressure. The final cleavage was done by stirring the peptide-resin in 10 mL of HF containing 1 mL of anisole and dithiothreitol (24 mg) at 0°C for 75 min. HF was removed by a flow of nitrogen. The residue was washed with ether (6 x 10 mL) and extracted with 4N HOAc (6 x 10 mL).

The peptide mixture in the aqueous extract was purified on a reversed-phase preparative high pressure liquid chromatography (HPLC) using a reversed phase Vydac™ C_{18} column (Nest Group, Southborough, MA). The column was eluted with a linear gradient (10% to 45% of solution B over 130 min.) at a flow rate of 10 mL/min (Solution A = 0.1% aqueous TFA; Solution B = acetonitrile containing 0.1% of TFA). Fractions were collected and checked on analytical HPLC. Those containing pure product were combined and lyophilized to dryness. 85 mg of a white solid was obtained. Purity was >99% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 3972.4 (in agreement with the calculated molecular weight of 3972.7).

The synthesis and purification of [Cha^{22}, $Leu^{23, 28, 31}$, Glu^{25}, $Lys^{26, 30}$, Ahc^{27}, Aib^{29}]hPTHrP(1-34)NH_2 was carried out in the same manner as the above synthesis of [$Glu^{22, 25}$, $Leu^{23, 28}$, $Lys^{26, 30}$, Aib^{29}, Ahc^{31}]hPTHrP(1-34)NH_2. The protected amino acid Boc-Cha-OH was purchased from Bachem, CA. The purity of the final product was >99%, and the electron-spray mass spectrometer gave the

molecular weight at 3997.2 (calculated molecular weight is 3996.8).

The full names for the abbreviations used above are as follows: Boc for t-butyloxycarbonyl, HF for hydrogen fluoride, Fm for formyl, Xan for xanthyl, Bzl for benzyl, Tos for tosyl, DNP for 2,4-dinitrophenyl, DMF for dimethylformamide, DCM for dichloromethane, HBTU for 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate, DIEA for diisopropylethylamine, HOAc for acetic acid, TFA for trifluoroacetic acid, 2ClZ for 2-chlorobenzyloxycarbonyl, and OcHex for O-cyclohexyl.

The substituents R_1 and R_2 of the above generic formula may be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., C_{1-12} alkyl, may be attached using reductive alkylation. Hydroxyalkyl groups, e.g., C_{1-12} hydroxyalkyl, may also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COE_1, may be attached by coupling the free acid, e.g., E_1COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for one hour and cycling the resulting resin through steps (a) to (f) in the above wash program. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

Other peptides of this invention can be prepared in an analogous manner by a person of ordinary skill in the art.

Functional Assays

A. Binding to PTH Receptor

The peptides of the invention were tested for their ability to bind to the PTH receptor present on SaOS-2 (human osteosarcoma cells). SaOS-2 cells (American Type Culture Collection, Rockville, MD; ATCC #HTB 85) were maintained in RPMI 1640 medium (Sigma, St. Louis, MO) supplemented with 10% fetal bovine serum (FBS) and 2 mM glutamine at 37°C in a humidified atmosphere of 5% CO_2 in air. The medium was changed every three or four days, and the cells were subcultured every week by trypsinization.

SaOS-2 cells were maintained for four days until they had reached confluence. The medium was replaced with 5% FBS in RPMI 1640 medium and incubated for 2 hrs at room temperature with 10 x 10^4 cpm mono-^{125}I-[Nle^{8,18}, Tyr^{34}(3-^{125}I)] bPTH(1-34)NH_2 in the presence of a competing peptides of the invention at various concentrations between 10^{-11}M to 10^{-4} M. The cells were washed four times with ice-cold PBS and lysed with 0.1 M NaOH, and the radioactivity associated with the cells was counted in a scintillation counter. Synthesis of mono-^{125}I-[Nle^{8,18}, Tyr^{34}(3-^{125}I)] bPTH(1-34)NH_2 was carried out as described in Goldman, M.E., et al., Endocrinol., 123:1468 (1988).

The binding assay was conducted with various peptides of the invention, and the Kd value (half maximal inhibition of binding of mono-^{125}I-[Nle^{8,18}, Tyr^{34}(3-^{125}I)]bPTH (1-34)NH_2) for each peptide was calculated.

As shown in Table I, all of the tested peptides had a high binding affinity for the PTH receptor on the SaOS-2 cell.

B. Stimulation of Adenylate Cyclase Activity

The ability of the peptides of the invention to induce a biological response in SaOS-2 cells were measured. More specifically, any stimulation of the adenylate cyclase was determined by measuring the level of synthesis of cAMP (adenosine 3',5'-monophosphate) as described previously in Rodan, et al., J. Clin. Invest.

72: 1511 (1983) and Goldman, et al., Endocrinol., 123:1468 (1988). Confluent SAOS-2 cells in 24 wells plates were incubated with 0.5 μCi [^{3}H]adenine (26.9 Ci/mmol, New England Nuclear, Boston, MA) in fresh medium at 37°C for 2 hrs, and washed twice with Hank's balanced salt solution (Gibco, Gaithersburg, MD). The cells were treated with 1 mM IBMX [isobutylmethyl-xanthine, Sigma, St. Louis, MO] in fresh medium for 15 min, and the peptides of the invention were added to the medium to incubate for 5 min. The reaction was stopped by the addition of 1.2 M trichloroacetic acid (TCA) (Sigma, St. Louis, MO) followed by sample neutralization with 4 N KOH. cAMP was isolated by the two-column chromatographic method (Salmon, et al., 1974, Anal. Biochem. 58, 541). The radioactivity was counted in a scintillation counter (Liquid Scintillation Counter 2200CA, PACKARD, Downers Grove, IL).

The respective EC_{50} values (half maximal stimulation of adenylate cyclase) for the tested peptides were calculated and shown in Table I. All tested peptides were found to be potent stimulators of adenylate cyclase activity, which is a biochemical pathway indicative as a proximal signal for osteoblast proliferation (e.g., bone growth).

TABLE I

PEPTIDE	Kd (μM)	EC_{50} (nM)
[Glu$^{22, 25}$, Leu$^{23, 28}$, Lys$^{26, 30}$, Aib^{29}, Ahc^{31}]hPTHrP(1-34)NH_2;	0.200	3.7
[Glu$^{22, 25}$, Ahc^{23}, Lys$^{26, 30}$, Leu$^{28, 31}$, Aib^{29}]hPTHrP(1-34)NH_2;	0.070	3.9
[Glu$^{22, 25}$, Leu$^{23, 28, 31}$, Lys$^{26, 30}$, Ahc^{27}, Aib^{29}]hPTHrP(1-34)NH_2;	0.230	3.0
[Glu$^{22, 25, 29}$, Leu$^{23, 28, 31}$, Lys^{26}, Ahc^{30}]hPTHrP(1-34)NH_2;	0.230	20
[Cha^{22}, Leu$^{23, 28, 31}$, Glu^{25}, Lys$^{26, 30}$, Ahc^{27}, Aib^{29}]hPTHrP(1-34)NH_2;	0.060	2.0
[Glu$^{22, 25}$, Leu$^{23, 28, 31}$, Ahc^{24}, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2;	0.006	0.5
[Glu$^{22, 29}$, Leu$^{23, 28, 31}$, Aib^{25}, Lys$^{26, 30}$, Ahc^{27}]hPTHrP(1-34)NH_2;		5
[Glu^{22}, Leu$^{23, 28, 31}$, Aib$^{25, 29}$, Lys$^{26, 30}$, Ahc^{27}]hPTHrP(1-34)NH_2;		2
[Ahe^{22}, Leu$^{23, 28, 31}$, Glu^{25}, Lys$^{26, 30}$, Aib^{29}]hPTHrP(1-34)NH_2		0.3
[Glu$^{22, 25}$, Leu$^{23, 31}$, Lys$^{26, 30}$, Ahe^{28}, Aib^{29}]hPTHrP(1-34)NH_2		0.5
[Cha^{22}, Ahe^{23}, Glu^{25}, Lys$^{26, 30}$, Leu$^{28, 31}$, Aib^{29}]hPTHrP(1-34)NH_2		0.4

Other Embodiments

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, that the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the claims.

What is claimed is:

1. A peptide of the formula:

$$R_1 \diagdown \quad A_1\text{-Val-}A_3\text{-Glu-}A_5\text{-Gln-}A_7\text{-}A_8\text{-His-Asn-}A_{11}\text{-}A_{12}\text{-Lys-His-}A_{15}\text{-} \quad \diagup R_2$$

$$A_{16}\text{-}A_{17}\text{-}A_{18}\text{-}A_{19}\text{-Arg-}A_{21}\text{-}A_{22}\text{-}A_{23}\text{-}A_{24}\text{-Arg-Lys-}A_{27}\text{-}A_{28}\text{-}A_{29}\text{-}$$

$$A_{30}\text{-}A_{31}\text{-}A_{32}\text{-}A_{33}\text{-}A_{34}\text{-}R_3,$$

wherein

A_1 is Ser, Ala, or Dap;

A_3 is Ser, Thr, or Aib;

A_5 is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe or p-X-Phe, in which X is OH, a halogen, or CH_3;

A_7 is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, or p-X-Phe in which X is OH, a halogen, or CH_3;

A_8 is Met, Nva, Leu, Val, Ile, Cha, Acc, or Nle;

A_{11} is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe or p-X-Phe in which X is OH, a halogen, or CH_3;

A_{12} is Gly, Acc, or Aib;

A_{15} is Leu, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, or p-X-Phe in which X is OH, a halogen, or CH_3;

A_{16} is Ser, Asn, Ala, or Aib;

A_{17} is Ser, Thr, or Aib;

A_{18} is Met, Nva, Leu, Val, Ile, Nle, Acc, Cha, or Aib;

A_{19} is Glu or Aib;

A_{21} is Val, Acc, Cha, or Met;

A_{22} is Acc or Glu;

A_{23} is Trp, Acc, or Cha;

A_{24} is Leu, Acc, or Cha;

A_{27} is Lys, Aib, Leu, hArg, Gln, Acc, or Cha;

A_{28} is Leu, Acc, or Cha;

A_{29} is Glu, Acc, or Aib;

A_{30} is Asp or Lys;

A_{31} is Val, Leu, Nle, Acc, Cha, or deleted;

A_{32} is His or deleted;

A_{33} is Asn or deleted;

A_{34} is Phe, Tyr, Amp, Aib, or deleted;

each of R_1 and R_2 is, independently, H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{7-20} phenylalkyl, C_{11-20} napthylalkyl, C_{1-12} hydroxyalkyl, C_{2-12} hydroxyalkenyl, C_{7-20} hydroxyphenylalkyl, or C_{11-20} hydroxynapthylalkyl; or one and only one of R_1 and R_2 is COE_1 in which E_1 is C_{1-12} alkyl, C_{2-12} alkenyl, C_{7-20} phenylalkyl, C_{11-20} napthylalkyl, C_{1-12} hydroxyalkyl, C_{2-12} hydroxyalkenyl, C_{7-20} hydroxyphenylalkyl, or C_{11-20} hydroxynapthylalkyl; and

R_3 is OH, NH_2, C_{1-12} alkoxy, or NH-Y-CH_2-Z in which Y is a C_{1-12} hydrocarbon moiety and Z is H, OH, CO_2H, or $CONH_2$;

provided that at least one of A_5, A_7, A_8, A_{11}, A_{12}, A_{15}, A_{18}, A_{21}, A_{22}, A_{23}, A_{24}, A_{27}, A_{28}, A_{29}, and A_{31} is Acc; or a pharmaceutically acceptable salt thereof.

2. A peptide of claim 1, wherein

A_3 is Ser;

A_5 is Ile or Acc;

A_7 is Leu, Acc, or Cha;

A_8 is Acc, Met, Nva, Leu, Val, Ile, or Nle;

A_{11} is Leu, Acc, or Cha;

A_{12} is Acc or Gly;

A_{15} is Leu, Acc, or Cha;

A_{16} is Asn or Aib;

A_{17} is Ser;

A_{18} is Acc, Met, or Nle;

A_{21} is Val or Acc;

A_{27} is Lys, hArg, Acc, or Cha;

A_{29} is Glu or Aib;

A_{31} is Val, Leu, Nle, Acc, or Cha;

A_{32} is His;

A_{33} is Asn;

A_{34} is Phe, Tyr, Amp, or Aib; and

or a pharmaceutically acceptable salt thereof.

3. A peptide of claim 2, wherein
A_5 is Ile or Ahc;
A_7 is Leu, Ahc, or Cha;
A_8 is Ahc, Met, or Nle;
A_{11} is Leu, Ahc, or Cha;
A_{12} is Ahc or Gly;
A_{15} is Leu, Ahc, or Cha;
A_{18} is Met or Ahc;
A_{21} is Val or Ahc;
A_{22} is Glu or Ahc;
A_{23} is Trp, Ahc, or Cha;
A_{24} is Leu, Ahc, or Cha;
A_{27} is Lys, hArg, Ahc, or Cha;
A_{28} is Leu, Ahc, or Cha;
A_{29} is Glu, Ahc, or Aib;
A_{31} is Val, Leu, Nle, Ahc, or Cha;
R_1 is H;
R_2 is H; and
R_3 is NH_2;
or a pharmaceutically acceptable salt thereof.

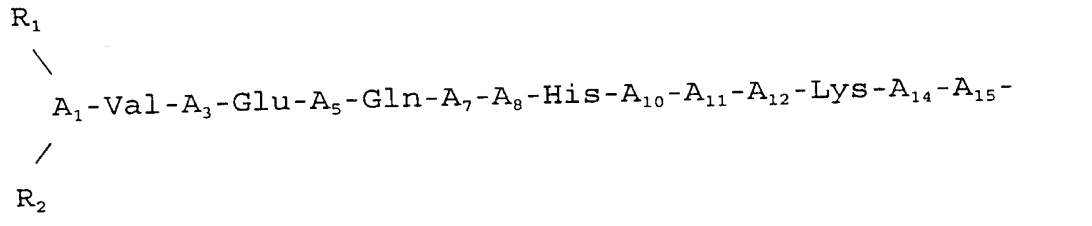
4. A peptide of claim 3, wherein at least one of A_7, A_{11}, A_{15}, A_{23}, A_{24}, A_{27}, A_{28}, or A_{31} is Cha.

5. A peptide of claim 3, wherein at least one of A_{16}, A_{17}, A_{19}, A_{29}, or A_{34} is Aib.

6. A peptide of claim 1, wherein said peptide is [$Ahc^{7,11}$]hPTH(1-34)NH_2; [$Ahc^{7,11}$, $Nle^{8,18}$, Tyr^{34}]hPTH(1-34)NH_2; [Ahc^{11}]hPTH(1-34)NH_2; [$Ahc^{7,11,15}$]hPTH(1-34)NH_2; [Ahc^{7}]hPTH(1-34)NH_2; [Ahc^{23}]hPTH(1-34)NH_2; [Ahc^{24}]hPTH(1-34)NH_2; [$Nle^{8,18}$, Ahc^{27}]hPTH (1-34)NH_2; [Ahc^{28}]hPTH(1-34)NH_2; [Ahc^{31}]hPTH(1-34) NH_2; [$Ahc^{24,28,31}$]hPTH(1-34)NH_2; [$Ahc^{24,28,31}$, Lys^{30}]hPTH(1-34) NH_2; [$Ahc^{28,31}$]hPTH(1-34)NH_2;

[Ahc^{15}]hPTH(1-34)NH_2; [Ahc^{24,27}, Aib^{29}, Lys^{30}]hPTH(1-34)NH_2; [Ahc^{24,27}, Aib^{29}, Lys^{30}, Leu^{31}]hPTH (1-34)NH_2; [Ahc^{5}]hPTH(1-34)NH_2; [Ahc^{12}]hPTH(1-34)NH_2; [Ahc^{27}] hPTH(1-34)NH_2; [Ahc^{29}]hPTH(1-34)NH_2; [Ahc^{24,27}]hPTH(1-34)NH_2; [Ahc^{24,27}, Aib^{29}]hPTH(1-34)NH_2; [Ahc^{24}, Aib^{29}]hPTH(1-34)NH_2; [Ahc^{27}, Aib^{29}]hPTH(1-34)NH_2; [Ahc^{18}]hPTH(1-34)NH_2; [Ahc^{8}]hPTH (1-34)NH_2; [Ahc^{18,27}, Aib^{29}]hPTH(1-34)NH_2; or [Ahc^{18,24,27}, Aib^{29}]hPTH(1-34)NH_2; [Ahc^{22}, Leu^{27}, Aib^{29}]hPTH(1-34)NH_2; [Ahc^{24}, Leu^{27}, Aib^{29}]hPTH(1-34)NH_2; [Ahc^{22}]hPTH(1-34)NH_2; [Ahc^{22}, Aib^{29}] hPTH(1-34)NH_2; or a pharmaceutically acceptable salt thereof.

7. A peptide of the formula:



wherein

A_1 is Ala, Ser, or Dap;

A_3 is Ser or Aib;

A_5 is His, Ile, Acc, or Cha;

A_7 is Leu, Cha, Nle, β-Nal, Trp, Pal, Acc, Phe, or p-X-Phe in which X is OH, a halogen, or CH_3;

A_8 is Leu, Met, Acc, or Cha;

A_{10} is Asp or Asn;

A_{11} is Lys, Leu, Cha, Acc, Phe, or β-Nal;

A_{12} is Gly, Acc, or Aib;

A_{14} is Ser or His;

A_{15} is Ile, Acc, or Cha;